Detecting the genomic signal of polygenic adaptation and the role of epistasis in evolution

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Abstract: Over the last decade, the genomic revolution has offered the possibility to generate tremendous amounts of data that contain valuable information on the genetic basis of phenotypic traits, such as those linked to human diseases or those that allow for species to adapt to a changing environment. Most ecologically relevant traits are controlled by a large number of genes with small individual effects on trait variation, but that are connected with one another through complex developmental, metabolic, and biochemical networks. As a result, it has recently been suggested that most adaptation events in natural populations are reached via correlated changes at multiple genes at a time, for which the name polygenic adaptation has been coined. The current challenge is to develop methods to extract the relevant information from genomic data to detect the signature of polygenic evolutionary change. The symposium entitled "Detecting the Genomic Signal of Polygenic Adaptation and the Role of Epistasis in Evolution" held in 2017 at the University of Zürich aimed at reviewing our current state of knowledge. In this review, we use the talks of the invited speakers to summarize some of the most recent developments in this field.

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Detecting the genomic signal of polygenic adaptation and the role of epistasis in evolution

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Over the last decade, the genomic revolution has offered the possibility to generate tremendous amounts of data that contain valuable information on the genetic basis of phenotypic traits, such as those linked to human diseases or those that allow for species to adapt to a changing environment. Most ecologically relevant traits are controlled by a large number of genes with small individual effects on trait variation, but that are connected with one another through complex developmental, metabolic and biochemical networks. As a result, it has recently been suggested that most adaptation events in natural populations are reached via correlated changes at multiple genes at a time, for which the name polygenic adaptation has been coined. The current challenge is to develop methods to extract the relevant information from genomic data to detect the signature of polygenic evolutionary change. The symposium entitled "Detecting the Genomic Signal of Polygenic Adaptation and the Role of Epistasis in Evolution" held in 2017 at the University of Zürich aimed at reviewing our current state of knowledge. In this review, we use the talks of the invited speakers to summarize some of the most recent developments in this field.

KEYWORDS
adaptation, evolutionary theory, experimental evolution, genomics, population genetics, quantitative genetics

1 | INTRODUCTION

Unravelling the mechanisms by which species adapt to environmental changes is a long-standing central goal of evolutionary genetics. Two fields have evolved relatively independently for decades using two radically different assumptions about the major mechanisms of evolutionary change. Population genetics focused on a "one locus for one trait" model and developed methods that use DNA sequence data to find regions of the genome that are under selection (so-called selective sweeps), while ignoring the phenotype. In contrast, quantitative genetics advocated an "infinitely many loci for one trait" model and built on the decomposition of phenotypic differences between relatives to predict evolutionary change, while ignoring the genotype. Both approaches have been extremely productive and greatly enhanced our understanding of evolution, mainly because they dealt with the two extreme mechanisms of evolutionary change that were mathematically (reasonably) tractable. While quantitative genetics followed Fisher (1918), who integrated Darwinian gradualism with Mendel's laws in a mathematical framework called the infinitesimal model, population genetics was motivated by early empirical evidence of the 1980s that pointed towards adaptation reached by either a new mutation or allele frequency changes at a single locus (see Orr, 2005 for a historical overview). The genomic revolution challenged these early observations, and it has become clear that mechanisms of adaptation are far more complex. In particular, the numerous recent genomewide association studies (GWAS) suggested that most quantitative and/or complex traits are controlled by many genes (e.g., Visscher et al., 2017), and selective sweeps are rather the exception than the rule (see, e.g., Hernandez et al.,

2011). Thus, population geneticists started to speculate that most adaptation events occur via subtle, potentially correlated, allele frequency shifts at many loci at a time for which the name polygenic adaptation has been coined (Pritchard & Di Rienzo, 2010; Pritchard, Pickrell, & Coop, 2010). Note that this "modern" polygenic adaptation has been motivated by genomic data and recognizes the importance of the dynamics of allele frequency changes in the course of adaptation, which is in contrast to the earlier polygenic views of evolution based on the fixation of mutations of small effects (Fisher, 1930; Orr, 2005). The main issue with polygenic adaptation is that it goes undetected with conventional statistical methods: frequency changes can be so small and the number of loci involved can be so large that with classical population genetic methods, the signature of selection is distinguishable from changes caused by drift. Further, most adaptation events may involve a mixture of selective sweeps and polygenic adaptation, making the statistical challenge even more acute. A solution may lie in borrowing methods from both population and quantitative genetics (Pritchard et al., 2010). Believing that the convergence of population and quantitative genetic theory and methods is a productive way of moving both fields forward, we organized the symposium entitled "Detecting the Genomic Signal of Polygenic Adaptation and the Role of Epistasis in Evolution" held on the 31 August and 1 September at the University of Zürich, Zürich, Switzerland.

Adding the role of epistasis to the programme seemed a necessary element: the action of many genes on a trait necessarily involves interactions between them. For decades, quantitative genetics argued for the relative unimportance of epistasis mainly because it was possible to accurately predict evolutionary changes of a trait while ignoring the epistatic variance component of the phenotype. Indeed, the effect of epistasis on variance components may be transitory: the elevated frequency of co-occurrence of beneficial allele combinations at different genes is expected to be continuously broken down by recombination. However, this view of epistasis ignores a fact known in molecular biology for a long time: genes affect the phenotype via complex interaction networks that impose a non-negligible effect of gene action on the phenotype (e.g., Hansen, 2013). The symposium offered a place for productive discussions and exchanges between evolutionary biologists from different fields on the role of epistasis in adaptation.

The symposium covered four different aspects of polygenic adaptation, each lasting a half-day, that we discuss in detail in the following paragraphs. The first session reviewed some of the most recent theoretical developments on polygenic adaptation and epistasis. The second session gave examples of studies that find evidence of polygenic adaptation and epistasis using the largest data sets currently available in humans, *Arabidopsis* and other species. The third session revealed findings of long-term breeding experiments in chickens and experimental evolution studies of microorganisms and nematodes on the role of epistasis. Finally, the fourth session gave an overview of some of the most recent statistical methods in population genetics aimed at detecting the signature of polygenic adaptation from genomic data.

2 | THEORY OF POLYGENIC ADAPTATION AND THE ROLE OF EPISTASIS IN ADAPTATION

Thomas Hansen opened the symposium with a plea for a better integration of epistasis, the "ugly duckling of evolutionary genetics," into quantitative genetics and evolutionary theory. He reminded us that genes do not work in isolation but interact through complex metabolic or signalling pathways. Yet, the classical, and dominant, view in quantitative genetics is to ignore the effects of gene interactions because epistatic effects are only partially transmitted from parents to offspring, and contribute little to the genetic variance of a trait, or only transiently so, through changes in linkage disequilibrium (Griffin, 1960; Kimura, 1965). This general view is backed up by the observation that most (but not all) of the genetic variance of a trait is contributed by its additive genetic component (e.g., Hill, Goddard, & Visscher, 2008). However, Hansen argued that this focus on the sole statistical decomposition of trait variance has been misleading because researchers in the field have not attempted to understand how the nature of gene interactions may influence the additive and nonadditive components of trait variance. He showed that the two components are in fact linked (Hansen & Wagner, 2001) and that epistasis affects the response to selection and the additive genetic variance of a trait under directional selection (Carter, Hermisson, & Hansen, 2005). One key insight from Hansen's theoretical work is that only directional epistasis is important for evolution in a way such that positive directional epistasis leads to increased evolvability, while negative directional epistasis leads to canalization. Directional epistasis can thus lead to the evolution of the additive effects of quantitative loci (Hansen, Álvarez-Castro, Carter, Hermisson, & Wagner, 2006) and have a permanent effect on the trait (in contrast to previous treatments that assumed no contribution of epistasis to additive effects; Griffin, 1960; Kimura, 1965). As additive effects of epistasis do not contribute to epistatic variance components, Hansen proposed to put less emphasis on the epistatic variance components that are too uninformative about the direction and sign of epistatic effects and to concentrate on the study of the structure of the genotype–phenotype map to understand how the nature of gene interactions affects evolution.

The talk of Nick Barton reminded us of the relevance of the infinitesimal model, originally formalized by Fisher (1918) (although named so later). The infinitesimal model (IM) postulates that a very large number of loci, each of very small effect, contribute to the variation of a quantitative trait. The properties of the IM are such that it accurately predicts the key features of trait inheritance already described by Francis Galton in the 19th century: regression to the mean and homoscedasticity of the offspring to (mid-)parent relation and its bivariate Gaussian distribution of trait values. Because allelic effects are assumed small, the distribution of allele frequencies under selection will not differ much from their neutral expectation, even if the accumulation of many slight allele frequency changes cause a change in the mean trait value. IM implies that alleles responsible for trait variation are under a selection

regime that is weak relative to random drift (Robertson, 1960). Thus, IM is likely to hold in small populations, but may also be valid in larger populations, when the number of loci is extremely large and each is under very weak selection, which seems to be the case as suggested by recent GWAS in humans (e.g., Visscher et al., 2017). When applied to multiple traits, IM imposes a limit to the number of traits that selection can optimize simultaneously, because average fitness is decreased by drift load by $1/4N_e$ per trait suggesting that the effective population size (N_e) imposes a limit to the complexity of organisms (Barton, Etheridge, & Veber, 2017). Barton concluded that this limitation seemed implausible and warrants further work to better understand how complex organisms evolve. Gene interactions can also be incorporated in IM. Paixão and Barton (2016) extended Robertson's work to allow for epistatic interactions and showed that when selection is strong relative to random drift the long-term trait response to selection is affected by epistasis if it is directional, in agreement with Hansen and colleagues. In fact, under such regime, the dynamics of allele frequencies depends exclusively on the structure of the genotype–phenotype map (Paixão & Barton, 2016).

Modern evolutionary genetics has been centred on the search for genomic signals of so-called selective sweeps; a characteristic pattern of reduced diversity expected to be created when one beneficial mutation rises rapidly in frequency in a population. However, such patterns proved to be rare in real data, suggesting that we may instead have to consider the action of many beneficial mutations on a trait (Pritchard & Di Rienzo, 2010). Joachim Hermisson presented a model, developed together with Pleuni Pennings and Ilse Hölliger, where they ask when to expect the process of (i) a sweep from a single new mutation (hard sweep), (ii) a sweep from multiple copies of a beneficial allele arising either from recurrent mutations or standing genetic variation (soft sweep) or (iii) polygenic adaptation meaning exclusively to adaptation characterized by small frequency shifts at many loci at a time (Hermisson & Pennings, 2017; see also Pritchard et al., 2010). They assumed that the trait under selection is affected by haploid biallelic equivalent loci with complete redundancy (i.e., many alternative loci can lead to the same trait value), which implies negative epistasis as for the case of stabilizing selection on a quantitative trait. They found that only the population genomic scaled mutation rate $\theta_g = 2N_eL\lambda\mu$ (with N_e = effective population size, L = number of loci, μ = per-locus mutation rate) determines which selection process is favoured, with adaptation from a single major locus when $\theta_g < 0.1$ (hard sweep at the locus with the highest frequency of the beneficial allele), major–minor locus pattern when $0.1 < \theta_g < 10$ (almost hard sweep at major locus and many partial sweeps at minor loci) and polygenic adaptation when $\theta_g > 10$ (super-soft sweeps or no sweep at all). Thus, for instance, polygenic adaptation is expected for a very polygenic trait with over 100 fully redundant loci, and locus-specific scaled mutation rate ($2N_e\mu$) of 0.1, yet polygenicity in itself does not preclude hard sweeps. Hermisson concluded with a call that a better understanding of functional epistasis in traits is necessary to understand patterns of adaptation.

3 | EVIDENCE FOR POLYGENIC SELECTION AND GENE INTERACTIONS FROM LARGE DATA SETS

Human genetics benefits from the largest GWAS panels available today, and Peter Visscher presented how these exceptional data sets can be used to detect the signature of selection on highly polygenic traits. He showed four examples, (i) evidence of polygenic adaptation to high altitude, including a new mixed model analysis method to detect evidence for selection (Yang et al., 2017); (ii) quantification of the relationship between effect size and heterozygosity in GWAS data; (iii) evidence for stabilizing selection in a contemporary population; and (iv) evidence that mean differences in complex trait values between populations are partially driven by natural selection (Zeng et al., 2017). The method of Zeng et al. (2017) is leveraging the relationship between the allele frequency and effect size of loci affecting the trait to estimate the direction and strength of selection. The proposed Bayesian method estimates the relationship between single nucleotide polymorphism (SNP) heterozygosity ($2p(1-p)$) and effect size (β) as $\beta \sim N(0, [2p(1-p)]^S\sigma^2_\beta)$ using all data simultaneously and accounting for linkage disequilibrium between SNPs, allowing a proportion of SNP to have zero effect size. The outcome of the model fitting is the overall polygenicity, which corresponds to the proportion of SNPs with nonzero effects, the heritability contributed by all SNPs when fitted together, and the selection parameter (S). When $S = 0$ ("neutral model") common and rare variants have similar effect sizes, so that most genetic variance comes from common variants (which have higher heterozygosity). In contrast, when $S < 1$ ("negative selection") rare, SNPs have bigger effects than common ones and all SNPs explain the same amount of variance. When $S = 1$ ("positive selection"), common variants have bigger effects. The authors used the UK Biobank database to simultaneously estimate SNP effects and genetic architecture parameters on a variety of traits and found that negative selection is pervasive in the human genome. Thus, most likely lower frequency variants tend to have larger effect size with deleterious effects on fitness through pleiotropy. Traits related to fertility (such as age at menopause) and heart function showed the strongest signal of negative selection and thus are likely to be strongly related to fitness. Peter Visscher concluded that it is slightly puzzling why so much genetic variation is found in fitness-related traits in humans, and emphasized the importance of multitrait analysis in future studies.

John McKay presented how a long-term field transplant experiment between two *Arabidopsis thaliana* ecotypes was able to elucidate some of the genetic details of adaptation to climate. Researchers produced recombinant inbred lines by crossing populations that inhabit drastically different climates (Sweden and Italy) for three consecutive years providing a unique opportunity to study the genetic background of local adaptation. Ågren, Oakley, McKay, Lovell, and Schemske (2013) demonstrated that relatively few genomic regions (15) of small to modest effect are responsible for much of the adaptive differentiation between the ecotypes, and some of them exhibit fitness trade-offs and epistatic interactions. Most

notably, one of the QTL was localized in a genomic region containing three transcription factors called C-repeat binding factors (CBFs) with a known functional role in freezing tolerance. This QTL exhibited a genetic trade-off: the nonlocal allele was deleterious in both environments. The authors concluded that a fitness trade-off associated with freezing tolerance genes is driving local adaptation between *Arabidopsis* populations diverged along a thermal gradient. To further address the generality of this finding, Monroe et al. (2016) surveyed CBF variation from 477 wild accessions collected across the species' range. They found that CBF sequence variation is strongly associated with winter temperature variables, thus suggesting that the disruption of CBF gene function is adaptive only in warm climate. This result illustrates how parallel evolution in a transcription factor can underlie adaptation to climate. Overall, these studies make unique examples of deciphering the evolutionary mechanisms of adaptation and emphasize the importance of an experimental approach that combines ecology, genomics and functional validation.

The lecture of Joshua L. Payne introduced the concept of an adaptive landscape in the context of gene regulation. The idea of an adaptive landscape dates back to the seminal work of Wright (1932), who first illustrated populations as a high-dimensional space of genotypes, each associated with a particular fitness. Natural selection moves populations towards fitness peaks. However, they are not always capable of reaching the highest peak, but can get stuck on a local optimum. Until recently, adaptive landscapes have been a tool used primarily in the context of theoretical models. Payne illustrated how a technology called protein binding microarrays facilitates the construction of adaptive landscapes from empirical data. He described a study by Aguilar-Rodríguez, Payne, and Wagner (2017), in which over a thousand adaptive landscapes were constructed and analysed. The surface of each landscape is the binding affinity of a transcription factor to all possible DNA sequences of a short length. Aguilar-Rodríguez et al. (2017) studied such landscapes from 129 eukaryotic species and contrasted them with two null models. First, a model with only additive interactions between nucleotides generates landscapes that almost always have a single adaptive peak, thus an evolutionary process should easily reach the global maximum. At the other extreme, binding affinities were randomly shuffled across all possible genotypes, generating a highly rugged landscape, upon which navigation by natural selection is challenging. Most empirical landscapes fell in between these two extremes. For example, the empirical landscapes contained more than one peak 42% of the time, with peak numbers ranging from two to 36. Further, epistasis, defined as nonadditive interactions between loci in their contribution to phenotype or fitness, played a role in shaping the topography of most empirical landscapes. Magnitude epistasis (i.e., when allelic effects do not simply add up but cause higher than predicted fitness) was almost as frequent as predicted by the shuffled model, and sign epistasis was also slightly more frequent than predicted by an additive model. Finally, they also showed that peaks were accessible by fewer mutations than predicted by the additive model. By comparing the topographies of these empirical landscapes with in vivo gene regulation data, Payne argued that the high navigability of these landscapes may have contributed to the enormous success of transcriptional regulation as a source of evolutionary adaptations and innovations.

4 | LESSONS FROM LONG-TERM BREEDING EXPERIMENTS AND EXPERIMENTAL EVOLUTION

Long-term selection experiments and laboratory evolution experiments have provided valuable insights into the genetic mechanisms underlying complex quantitative traits and the influence of epistasis on evolutionary processes. Örjan Carlborg opened the Friday morning session by presenting several empirical examples highlighting the role of epistasis in the genetic architecture of complex traits. First, he presented the results from a long-term experimental selection experiment in chicken. Carlborg, Jacobsson, Åhgren, Siegel, and Andersson (2006) used epistatic QTL mapping to show how body weight evolution in chicken is determined by the combination of beneficial alleles at multiple interacting loci and not by an individual genetic effect of a single major locus, as previously thought. Using the chicken example, Carlborg introduced an analytical model based on visualizing statistically significant epistatic QTLs through networks in which nodes represent QTLs and edges represent interactions between them. One observed network topology consists in a central hub QTL connected to multiple other QTLs. Carlborg illustrated how these radial epistatic networks have been useful to study the genetic mechanisms determining complex trait variation, such as root length in *Arabidopsis thaliana* (Lachowiec, Shen, Queitsch, & Carlborg, 2015), body weight in chicken (Carlborg et al., 2006) and multiple quantitative traits in yeast (Forsberg, Bloom, Sadhu, Kruglyak, & Carlborg, 2017). He also highlighted that central hub QTLs are important because they act as genetic capacitors that can both buffer and release cryptic genetic variation affecting the total level of phenotypic variation in populations. For example, networks of capacitating genetic interactions in yeast contribute to more variation—both additive and nonadditive—(Forsberg et al., 2017) than previously estimated (Bloom et al., 2015). In conclusion, nonadditive allelic effects are important and need to be taken into account when studying the genetic mechanisms that generate trait variation and predicting the response to selection to long-term selection experiments.

Epistasis is pervasive in microbial and viral populations. Microbial populations have low levels of recombination, which prevent the reshuffling of beneficial mutations and their interactions. Sergey Kryazhimskiy presented results from two yeast evolution experiments designed to test how epistasis and historical contingency affect the predictability of adaptation. In the first experiment, Kryazhimskiy, Rice, Jerison, and Desai (2014) evolved 640 populations starting from closely related genotypes and found that initially less fit genotypes adapted faster than those that were initially fitter. Genetic analyses revealed that all populations sampled mutations

from a common pool of adaptive mutations and that at least some adaptive mutations that drove adaptation exhibited diminishing-returns epistasis, that is, they had smaller beneficial effects in fitter backgrounds, which would explain the observed decline in "adaptability" with increasing initial fitness. In the second part of his talk, Kryazhimskiy presented results from a recent analogous experiment where they evolved 1840 populations starting from 230 founders derived from a cross between two divergent yeast strains (Jerison et al., 2017). Consistent with the previous study, Jerison et al. (2017) observed that "the rule of declining adaptability" continues to hold. They also found one QTL that dramatically shifts the spectrum of adaptive mutations. Kryazhimskiy concluded his talk by saying that adaptability is a heritable and predictable trait and distinguished between two types of epistasis: the one in which the beneficial effects of mutations depends on fitness (i.e., diminishing-returns epistasis) and the one where rare mutations alter the whole spectrum of further adaptive mutations.

Finally, Luke Noble presented another experimental system in which epistasis is important: an experimentally evolved populations of the nematode *Caenorhabditis elegans* (Noble et al., 2017). Noble et al. (2017) generated parental populations from multiple intercrosses of 15 wild isolates and a domesticated laboratory strain of *C. elegans*. Parental populations were evolved for 250 generations of effective outcrossing, and 507 recombinant inbred lines (RILs) were generated. Then, they sequenced the parental populations and the 507 RILs to explore the genetic basis of two fitness components: fertility and body size. This analysis revealed that large-effect sign epistasis and polygenic interactions contributed much of the trait variance, particularly to variance in fertility (defined in such a way as to be closely aligned with fitness during experimental evolution). Noble emphasized the importance of modelling epistasis for predicting phenotypes, particularly in systems where divergently adapted alleles may be segregating, which agrees with the conclusions from other speakers from this session.

5 | STATISTICAL METHODS TO DETECT THE GENOMIC SIGNAL OF POLYGENIC ADAPTATION

Adaptation to climate is considered a highly polygenic trait. Therefore, the evolution of similar molecular mechanisms in different species in response to similar climatic conditions is thought to be rather unlikely. Sam Yeaman showed the opposite in his study with two distantly related conifer species, lodgepole pine and interior spruce (Yeaman et al., 2016). He and his colleagues found a large set of genes—much larger than expected by chance—that showed the same associations between allele frequencies and similar environmental gradients in the two tree species that separated 140 Million years ago. One of the major challenges in the analysis was the correction for neutral population structure. In the case of interior spruce, the neutral genetic pattern correlated with the climatic gradient, leading to the almost complete disappearance of the adaptive signal in environmental association approaches that correct for neutral population structure. They therefore decided not to include neutral population structure, but concentrated on the common adaptation signals of the two species, because false positives due to random processes like drift are unlikely to be found in both species. They concluded that due to genetic constraints, some detectable large-effect loci (i.e., key genes) must be present even in the complex polygenic adaptation to climate.

Gene networks may play a central role in the development of statistical methods to detect polygenic adaptation. Josephine Daub presented the "Polysel" approach (Daub et al., 2013; Daub, Moretti, Davydov, Excoffier, & Robinson-Rechavi, 2017) to search for gene sets that are significantly enriched for selection signals. Instead of performing a gene ontology enrichment test on a priori detected loci under selection, her method considers the functional information before performing a test for selection. Thus, even small allele frequency shifts, if present in several functionally connected genes, can be detected. The approach requires test statistics for each locus derived from any single locus tests for selection (e.g., FST-based outlier test or environmental association analysis) and information about gene pathways, such as the KEGG (Kanehisa, Furumichi, Tanabe, Sato, & Morishima, 2017) and Reactome (Fabregat et al., 2015) databases, which are publicly available. Then, a SUMSTAT score is calculated for each gene set, which is simply the sum of the gene-level selection scores of the gene set. The significance of the SUMSTAT score is assessed with a null distribution of random gene sets, taking into account gene set size and SNP density per gene. Josephine Daub demonstrated several cases, where the above-described method revealed previously undiscovered signatures of selection, and showed that in humans most enriched gene pathways are involved in immune responses (Daub et al., 2013). Further, among the members of these pathways, there was strong evidence for epistatic interactions.

Finally, Jeremy Berg, author of one of the first methods to detect polygenic adaptation from genomic data (Berg & Coop, 2014), presented two recent studies on detecting the signature of polygenic adaptation in humans. In the first study, the authors tested for polygenic adaptation among human populations worldwide by comparing polygenic scores calculated from GWAS to their null distribution under genetic drift, and they identified strong signals of selection for a suite of anthropometric traits including height, infant head circumference, hip circumference, waist-to-hip ratio, as well as type 2 diabetes (Berg, Zhang, & Coop, 2017). Additionally, some of the body traits followed a strong latitudinal cline in Western Eurasia, consistent with thermoregulatory adaptation in response to latitudinal temperature variation. In the second study, the authors developed a method, called "PolyGraph," to detect polygenic adaptation in admixture graphs, where historical divergences and admixture events connect different populations through time (Racimo, Berg, & Pickrell, 2018). The authors found evidence that variants associated with several traits, including height, educational attainment and self-reported unibrow, have been influenced by polygenic adaptation in different human populations.

6 | CONCLUSIONS

The symposium attracted over 100 participants, many from overseas, indicating a high interest in polygenic adaptation and epistasis. Nine additional participant talks and 23 poster presentations contributed to a diverse and productive event (Appendix S1). Putting together the conclusions of the different presentations, two clear messages arose. First, although many studies provide evidence of polygenic trait architecture suggesting that the polygenic mode of adaptation may be frequent, it remains unclear whether and how often traits are in the polygenic adaptation regime described by Hermisson and colleagues. It is also unclear whether we are truly able to detect the signature of slightly correlated shifts in allele frequencies, and even so, under what conditions and with what kind of data. There is accumulating evidence from the largest genome-wide association panels in humans, as illustrated by Peter Visscher and Jeremy Berg, that most quantitative traits are influenced by hundreds or thousands of loci. On the one hand, these results stress that the infinitesimal model may be a good approximation for most traits that play a role in adaptations in natural populations, thus suggesting that evolutionary quantitative genetic theory will continue to be useful. On the other hand, it fundamentally questions the reductionist approach of population genetics of trying to find the signature of selection at individual genes underlying adaptations from genomic data. Further, detecting small but correlated changes in allele frequencies proves to be extremely difficult and may only be possible with the help of additional data (such as functional and/or phenotypic or replicated data sets), as illustrated by the talks of Josephine Daub and Sam Yeaman. Further, the talks of Joachim Hermisson, Sam Yeaman and Jeremy Berg also emphasized that the task of detecting polygenic adaptation, or the signature of any other kind of selection, requires an understanding of population demography and structure.

Second, there was a consensus among most participants that epistasis needs more attention and that a shift in focus from variance components to the genotype–phenotype map is necessary. Experimental evolution studies in model species provide compelling evidence that epistasis is pervasive, as illustrated by the talks of Sergey Kryazhimskiy and Luke Noble. Örjan Carlborg further illustrated that in more complex organisms, epistasis may become a necessary element to explain part of the phenotypic variance. Moreover, GWAS have often shown that it remains difficult to explain the totality of trait variance, even with the largest possible samples, as illustrated by the case of human height, where still only 45% of the family heritability is explained despite gigantic sample sizes (e.g., Yang et al., 2010), leaving the door open for gene interactions as a possible explanation. The challenge now is to link studies focusing on the details of complex molecular systems with quantitative genetics to understand how those details are integrated into phenotypic variation. Translating the complexity of interactions into system properties should allow us to better understand and describe the structure of the genotype–phenotype map.

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AUTHOR CONTRIBUTION

The authors organized the symposium and attended all sessions. K.C. wrote part 3, A.R.-V. wrote part 4, C.R. wrote part 5, F.G. wrote part 2. K.C. and F.G. wrote parts 1 & 6.

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